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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,188	06/05/2000	JAN DROUAUD	065691/0184	8841

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EXAMINER	
BAUM, STUART F	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 11/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/509,188	DROUAUD ET AL.	
	Examiner	Art Unit	
	Stuart F. Baum	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10 and 12-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10 and 12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *with application* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

RCE Acknowledgment

1. The request filed on July 24, 2003 for a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114, based on parent Application No. 09/509188 is acceptable and a RCE has been established. An action on the RCE follows.

2. Claims 1, 3-10, and 12-19 are pending and are examined in the present office action.

Claim 2 has been canceled.

Claim 19 has been newly added.

3. The amendment is improper because claim 3 depends on canceled claim 2. Correction is required.

Claim Objections

Claims 3, 8, and 15 are object to for the following issues:

4. Claim 3 is objected to for depending on a canceled claim. For reasons of compact prosecution, claim 3 will be examined as if it depends from claim 1. Acknowledgment is required.

5. In claim 8, 3rd line, "linked" is misspelled.

6. Claim 15 is missing from Applicants' amendment and it is believed to be an inadvertent over-sight. For reasons of compact prosecution, claim 15 will be examined, as it appeared in the pre-amendment filed 8/18/2000. Acknowledgment is required.

Specification

7. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required. It is noted in the amendment filed 12/13/2002, that Applicant states that an abstract on a separate sheet is attached, but no such attachment is found.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 3-7, 9, and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection includes dependent claims.

In claim 1, it is recommended that the word "homology" be replaced with --sequence identity--. The meaning of the word "homology" is indefinite as it is not clear how relatedness is determined, whether by sequence relatedness alone, by evolutionary relatedness, or by some other means. All subsequent recitations of "homology" are also rejected.

In claim 3, the metes and bounds of "cytotoxic product" have not been defined. It is unclear what constitutes a cytotoxic product. Applicant has not defined the threshold toxicity level that delineates a product that is toxic compared with another product that is not toxic. All subsequent recitations of "cytotoxic product" are also rejected.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 3-10, and 12-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a nucleotide sequence which has at least 80% sequence identity with nucleotides 1-2056 of SEQ ID NO:3 or a fragment of a nucleotide sequence which either has at least 80% sequence identity with nucleotides 1-2056 of SEQ ID NO:3 or a fragment of a nucleic acid comprising nucleotides 1-2056 of SEQ ID NO:3, a vector comprising one of said sequences upstream of a nucleic acid encoding any cytotoxic product, and plant comprising said vector or a method for producing a gametophytic male sterile plant with inducible fertility comprising a fragment of the promoter which consists essentially of nucleotides 1-2056 of SEQ ID NO:3 or a sequence which hybridizes to nucleotides 1 to 2111 of SEQ ID NO:3 or a sequence which has at least 80% sequence identity to nucleotides 1-2111 of SEQ ID NO:3 or a sequence which hybridizes to nucleotides 1-2111 of SEQ ID NO:3 all of which are operably linked to a gene encoding any cytotoxic product wherein the cytotoxic product is a subtilisin.

The Applicants isolated their invention from a subtraction hybridization between cDNA libraries constructed from fertile floral tissue of rape and male sterile rape. Putative clones were used to screen a microspore library and one of the resulting clones was used to screen a genomic

library purchased from CLONETECH Laboratories, Inc. Clone BnM3.2 (SEQ ID NO:3) was isolated and the promoter sequence was used to construct a cassette comprising said promoter sequence and the beta-glucuronidase gene. Transformation experiments with said construct yielded plants exhibiting GUS expression specifically in the microspores.

The Applicants isolated a promoter consisting of nucleotides 1-2056 of SEQ ID NO:3 (page 12, lines 23-28) and demonstrated that it specified expression in microspores of *Arabidopsis* (page 13, lines 16-19), but they do not identify structural features unique to the promoter consisting of nucleotides 1-2056 of SEQ ID NO:3. In addition, the Applicants do not identify the functional domains of the promoter nor the cis-acting elements that are required for proper spatial expression in microspores. In addition, the Applicants do not specify nor describe a gene encoding a male-gamete-specific cytotoxic product nor do they describe a subtilisin protease. The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See Fiers vs. Sugarno, 25 USPQ2d (CAFC 1993) at 1606, which states that "[a]n adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself". In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Given the lack of description, it remains unclear what features identify the promoter exhibiting 80% sequence identity to nucleotides 1-2056 of SEQ ID NO:3, or a sequence that hybridizes to a nucleic acid molecule comprising 1-2111 of SEQ ID NO:3 or a fragment thereof

or any sequence encoding a cytotoxic product or encoding any subtilisin. Since Applicants' promoter, cytotoxic product or subtilisin have not been described by specific structural features, the specification fails to provide an adequate written description to support the broadly claimed invention.

Response to Applicant's remarks concerning Written Description

Applicants contend in the amendment filed July 24, 2003 that it is well established in the art that certain transcription factors bind to specific sequences present in eukaryotic promoters. One such region is the TATA box (page 7, 1st full paragraph). Applicants also contend that finding transcription start sites are known (page 7, 2nd paragraph) and that there exists a wealth of literature from which the skilled artisan can retrieve basic and detailed information for determining which portions or fragments of SEQ ID NO:3 are likely to be involved in transcription of a gene. Applicants further contend that it is now routine practice, and certainly not undue experimentation, to create "promoter deletion constructs" operably linked to a reporter gene, in order to determine which regions or fragments of a promoter are required for transcription (page 8, 1st full paragraph).

The Office contends that Applicant is arguing the Enablement rejection, i.e., routine experimentation versus undue experimentation. The issue at hand, is that Applicant has not described a representative number of promoter sequences that are encompassed by the claims. Applicant has not described structural features common to and unique to the claimed genus of promoters. In regards to known regions, a "TATA" box is not unique to the genus of Applicants' claimed promoters. It takes more than just the TATA box to produce a viable promoter sequence.

Scope of Enablement

10. Claims 1, 3-10, and 12-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a promoter sequence consisting essentially of nucleotides 1-2056 of SEQ ID NO:3 operably linked to a nucleic acid sequence encoding a protein, transformed into a plant from the Brassicaceae family, wherein said promoter sequence drives expression in microspores, does not reasonably provide enablement for claims broadly drawn to a nucleotide sequence which has at least 80% sequence identity with nucleotides 1-2056 of SEQ ID NO:3 or a fragment of a nucleotide sequence which either has at least 80% sequence identity with nucleotides 1-2056 of SEQ ID NO:3 or a fragment of a nucleic acid comprising nucleotides 1-2056 of SEQ ID NO:3, a vector comprising one of said sequences upstream of a nucleic acid encoding any cytotoxic product, and plant comprising said vector or a method for producing a gametophytic male sterile plant with inducible fertility comprising a fragment of the promoter which consists essentially of nucleotides 1-2056 of SEQ ID NO:3 or a sequence which hybridizes to nucleotides 1 to 2111 of SEQ ID NO:3 or a sequence which has at least 80% sequence identity to nucleotides 1-2111 of SEQ ID NO:3 or a sequence which hybridizes to nucleotides 1-2111 of SEQ ID NO:3 all of which are operably linked to a gene encoding any cytotoxic product wherein the cytotoxic product is a subtilisin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Applicants isolated their invention from a subtraction hybridization between cDNA libraries constructed from fertile floral tissue of rape and male sterile rape. Putative clones were used to screen a microspore library and one of the resulting clones was used to screen a genomic

library purchased from CLONETECH Laboratories, Inc. Clone BnM3.2 (SEQ ID NO:3) was isolated and Applicants further isolated the corresponding promoter consisting of nucleotides 1-2056 of SEQ ID NO:3 (page 12, lines 23-28) and demonstrated that it specified expression in microspores of *Arabidopsis* (page 13, lines 16-19) by operably linking the promoter to the beta-glucuronidase gene.

The Applicants are claiming a sequence of DNA that expresses in microspores and a method of making male sterile plants with inducible fertility but Applicants have only demonstrated that nucleotides 1-2056 of SEQ ID NO:3 direct expression of a nucleic acid sequence encoding a protein in microspores of a Brassicaceae plant. Applicants have not demonstrated that a fragment of the above sequence, or a sequence that either exhibits 80% sequence identity to the above sequence or that hybridizes to nucleotides 1-2111 of SEQ ID NO:3 will also direct expression in the same pattern as nucleotides 1-2056 of SEQ ID NO:3. In addition, because Applicants have not explicitly defined what is meant by "a cytotoxic product" as discussed above, and because they have not exemplified any "cytotoxic product" or any "cytotoxic product" that is a subtilisin that is lethal to developing microspores when expressed therein, or any "cytotoxic product" that can be inhibited by an insecticide molecule of the fluorophosphates family, Applicants have not reduced to practice their broadly claimed invention.

Applicants have claimed fragments, and sequences exhibiting less than 100% sequence identity to nucleotides 1-2056 of SEQ ID NO:3, but the state-of-the-art teaches non-coding nucleic acid sequences that exhibit base pair deletions, substitutions or rearrangements, cannot be expected to maintain their promoter or enhancer activity. Izawa et al (1993, J. Mol. Biol.

230 :1131-1144) teach that the nucleotides flanking the G-box (CACGTC) and C-box (GACGTC) hexameric cores were shown to affect protein binding activity and specificity of bZIP transcription factors (page 1132, bottom of right column; page 1134, bottom of left column). Hao, et al (1998, The J. of Biological Chemistry 273 (41): 26857-26861) investigated the binding activities of ethylene-responsive element-binding proteins (EREBP) to their cis-element GCC box (AGCCGCC). Creating base-pair substitutions within the GCC box modulates binding specificity, implying that different positions within the GCC box are important for differential binding by different EREBP's, in particular, substituting T's for the two G's eliminates binding completely (*supra*, pages 26857, abstract and 26860, left column, 2nd paragraph).

Even though the Applicants are not utilizing intronic regions to help specify microspore expression, the molecular mechanism of transcription for intronic regions is the same as 5' promoter regions. Busch et al (1999, Science 285:585-587) and Lohmann et al (2001, Cell 105 :793-803) teach that *LEAFY* (*LFY*) and *WUSCHEL* (*WUS*), which have been shown to be transcription factors that together activate proper *AGAMOUS* (*AG*) expression, do so by binding to the second intron of the *AG* gene. A two base-pair mutation within the binding site of either *LFY* or *WUS* eliminates binding of either *LFY* or *WUS*, respectively (Busch et al (supra) page 587 left column, 2nd paragraph; Lohmann et al (supra) page 799, bottom and top of left and right columns) and changes the temporal and spatial *AG* expression pattern.

Applicants claim a sequence isolated by hybridization techniques in which the hybridization conditions are not specified. The state-of-the-art teaches DNA fragments isolated using even stringent conditions do not always select for DNA fragments whose contiguous

nucleotide sequence is the same or nearly the same as the probe. Fourgoux-Nicol et al (1999, Plant Molecular Biology 40 :857-872) teach the isolation of a 674bp fragment using a 497bp probe incorporating stringent hybridization conditions comprising three consecutive 30 minute rinses in 2X, 1X and 0.1X SSC with 0.1% SDS at 65^{0}C (page 859, left column, 2nd paragraph). Fourgoux-Nicol et al also teach that the probe and isolated DNA fragment exhibited a number of sequence differences comprising a 99bp insertion within the probe and a single nucleotide gap, while the DNA fragment contained 2 single nucleotide gaps and together the fragments contained 27 nucleotide mismatches. Taking into account the insertions, gaps and mismatches, the longest stretch of contiguous nucleotides to which the probe could hybridize consisted of 93bp of DNA (page 862, Figure 2). In the present example, the isolated fragment exhibits less than 50% sequence identity with the probe.

Applicants claim a method of producing male sterile plants comprising overexpressing a subtilisin in microsporocytes. The state-of-the-art teaches that mircosporocytes already comprise a subtilisin. Taylor et al (1997, The Plant Journal 12(6):1261-1271) teach that a serine proteinase which is a member of the subtilisin-related proteins (page 1268, left column, last paragraph) is detected in both tapetal cells of the anther and in microsporocytes (page 1268, left column, 2nd paragraph). The state-of-the-art brings into question the use of a subtilisin to create non-viable microsporocytes. In addition, not all subtilisin proteins are alike. Jorda et al (2000, Plant Physiology 122 :67-73) teach that there are five distinct subfamilies of subtilase genes in plants (page 67, right column, 1st paragraph). Jorda et al teach that the P69E and P69F genes which are members of the p69 family, have different developmental roles compared to other family members (page 72, right column, 3rd paragraph).

Applicants' claims are drawn to a method for producing a male sterile plant due to the action of a subtilisin, whose activity is inhibited by the application of a fluorophosphate chemical. Travis et al (June, 2002, U.S. Patent 6,399,759) teaches that diisopropyl fluoropohosphate is a general serine class inhibitor (abstract). Jorda et al teaches that plants have endogenous serine proteases (abstract) and Segarra et al (2003, Journal of Experimental Botany 54(386):1335-1341) teach that plants also have a serine protease inhibitor (abstract). In addition, Baker et al (1992, Pesticide Science 34(2):167-182) teach that chemical insecticides are absorbed into the plant at different rates depending on the surfactant and the concentration of the surfactant (abstract). Applicants' method comprises applying a general serine protease inhibitor to a plant that endogenously comprises many serine proteases and even comprises a protease inhibitor. Applicants need to teach by way of guidance or examples the precise conditions required to execute the claimed method, given the preponderance of evidence that points out all the obstacles that will generate unexpected results.

Given the state-of-the-art, claim breadth, unpredictability and lack of guidance as stated above; given the breadth of the claims which encompass a multitude of sequences that have not been exemplified; it would require undue experimentation by one skilled in the art to identify and isolate a multitude of non-exemplified promoter fragments that express in microspores and to operably link the promoter fragment to a multitude of nucleic acid molecules that encode a cytotoxic product whose activity is inhibited by a fluorophosphates chemical that can be absorbed into the plant, and to evaluate the ability of all these factors to cause the claimed effects in plants transformed therewith.

Response to Applicant's remarks concerning Enablement

Applicants contend in the amendment filed July 24, 2003, that it is not necessary to explain how the cytotoxic product promotes an adverse affect on a microspore (page 10, 2nd paragraph from the bottom), nor is it necessary to elucidate the mechanism by which their invention works (page 11, 2nd paragraph). Applicants further contend that the Office has not provided examples or references specific to the assertion that microspores already comprise the subtilisin protein. In addition, Applicants also contend that "lack of experimental data" is not sufficient grounds for rejecting Applicants' claimed invention (page 11, middle paragraph). Lastly, Applicants contend that the rejection is flawed because plants have "subtilisin-like" proteases and not *bona fide* bacterial "subtilisin" (page 11, last paragraph).

The Office contends that all subtilisins or subtilisin-like proteins from plants are proteases that are inhibited by fluorophosphates, given the lack of information to the contrary. In addition, given the preponderance of evidence presented in the present office action with respect to the unpredictability in the state-of-the-art, undue trial and error experimentation would be required to practice the claimed invention, without further guidance or examples.

Applicants contend in the amendment filed July 24, 2003, that the scientific literature is replete with information regarding the species-to-species differences in plant cuticular composition and permeability (page 12, 3rd paragraph) and there is no basis for rejection of claims drawn to applying an insecticide to transformed plants.

The Office contends that the literature is replete with articles dealing with absorption of herbicides into plants for the purpose of killing the plant, and not the absorption of a fluorophosphate chemical for the purpose of inactivating a specific protease. Applicants'

invention is drawn to a method of inhibiting the activity of a protease in a very specific structure of the plant. This requires that the chemical be absorbed into the plants' symplast and be specifically translocated to the developing microspores, which are encased in the locules of the anthers. All of this has to occur at the correct developmental time so that the introduced subtilisin can be inactivated, thereby allowing the developing microspores to complete their development without the introduced protease destroying the micropores proteins.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

11. Claim 7 is rejected under 35 U.S.C. 102(e) as being anticipated by Cigan et al (filed Jan. 7, 1995, U.S. Patent Number 5,689,049).

The claim is drawn to a plant having gametophytic male sterility with inducible fertility, comprising a gene encoding any cytotoxic product which is linked to any male-gamete-specific promoter. Claim 7 does not recite any particular nucleic acid sequence.

Cigan et al teach a method of producing male sterile plants comprising transforming a plant with an expression vector comprising a methylase gene operably linked to a promoter that specifically directs expression in the anthers. Promoter methylation by the methylase gene can cause gene inactivation and alter the phenotype in transgenic organisms (column 3, 5th paragraph) and as such will act as a cytotoxin to disrupt the normal development of the cell in which the methylase is expressed. Cigan et al also teach a method for reversing the infertility caused by the methylase gene by including in the promoter operably linked to the methylase gene an operator sequence on which binds a LexA repressor (column 5, 2nd paragraph). The gene encoding the LexA repressor is operably linked to an inducible promoter and transformed into plants comprising the methylase construct. Having both the methylase and LexA constructs in one plant creates a plant and method for inducing male sterility. Given that the claim does not recite a specific sequence, and given that Applicants do not define a male-gamete-specific promoter, Cigan et al anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 7, 12, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cigan et al (filed Jan. 7, 1995, U.S. Patent Number 5,689,049) taken with Zou et al (1997, The Plant Cell 9:909-923).

The claims are drawn to a plant having gametophytic male sterility with inducible fertility, comprising a gene encoding any cytotoxic product which is linked to any male-gamete-specific promoter, or wherein the plant is from the family Brassicaceae or wherein the plant is rape. Claim 7 does not recite any particular nucleic acid sequence.

The teachings of Cigan et al have been discussed above.

Cigan et al do not teach rape transformation.

Zou et al teach rape transformation.

Given the recognition of those of ordinary skill in the art of the value of producing a plant having male sterility with inducible fertility as taught by Cigan et al, and given the disclosure of Zou et al that teach successful transformation of *Brassica napus* (rape), it would have been obvious to use the method as taught by Cigan et al and to combine this method with the teachings of Zou et al to produce stably transformed rape plants.

Thus the claimed invention would have been *prima facie* obvious as a whole to one of ordinary skill in the art at the time it was made, especially in the absence of evidence to the contrary.

13. Claims 1, 3-6, 8-10, 13-14, and 16-19 are deemed free of the prior art, given the failure of the prior art to teach or reasonably suggest a plant comprising an isolated nucleotide sequence

consisting essentially of nucleotides 1-2056 of SEQ ID NO:3, or a sequence which has at least 80% sequence identity with nucleotides 1-2056 of SEQ ID NO:3 or a fragment thereof, and wherein said sequence is capable of expressing a second nucleotide sequence to which it is operably linked and wherein said sequence is a gametophytic-specific promoter; a vector comprising said sequence upstream of a DNA sequence encoding a cytotoxic product; and a method for producing a plant with gametophytic male sterility with inducible fertility comprising transforming a plant with said vector in which the cytotoxic product is a subtilisin and the inducible fertility is caused by applying an insecticide molecule of the fluorophosphates family to said plant.

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart F. Baum whose telephone number is 703-305-6997. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 703-306-3218. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Stuart F. Baum Ph.D.

November 3, 2003

AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600